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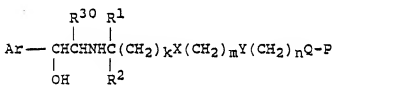
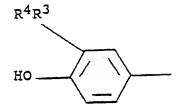
(54) **Ethanolamine derivates, processes for their preparation and pharmaceutical compositions containing them.**

(57) This invention relates to compounds of the general formula (I)

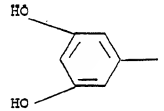


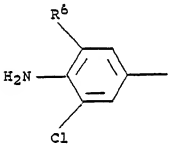
(I)

and physiologically acceptable salts and solvates thereof where
Ar represents

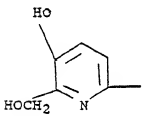
(a) 

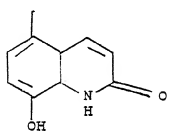
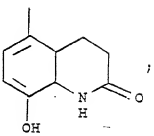
where
R^3 is a bond or a straight or branched C_{1-2}alkylene group,
R^4 is a hydroxy group or a group R^5NH-where
R^5 represents a group CH_3SO_2-, HCO-or NH_2CO-,

(b) 

(c) 

where R^6 is a chlorine atom or the group F_3C-,

(d) 

(e)  or 

k represents an integer from 1 to 8.

m represents zero or an integer from 2 to 7 and

n represents an integer from 2 to 7 with the proviso that the sum total of k, m and n is 4 to 12;

R^1 and R^2 each represents a hydrogen atom or a methyl or ethyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 2;

R^{30} represents hydrogen or C_{1-2}alkyl;

X represents an oxygen or sulphur atom; and

Y and Q may each represent a bond or an oxygen or sulphur atom with the provisos that at least one of Y and Q represents an oxygen or sulphur atom and when Y is a bond m is zero, or when Y represents an oxygen or sulphur atom m is an integer from 2 to 7;

P represents a phenyl group otionally substituted by one or more substituents selected from halogen atoms, or the groups C_{1-3}alkyl, C_{1-3}alkoxy, hydroxy, $-CH_2OH$-, $-(CH_2)_2CH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2(CH_2)_2CH_3$, $-R^7$, COR^7, $-NHCOR^8$ and $-NR^9SO_2R^{10}$;

where

R^7 represents an amino, aminoC_{1-3}alkyl, aminoC_{1-3}dialkyl, pyrrolidino, piperidino, hexamethyleneimino, piperazino, N-methylpiperazino or morpholino group;

R^8 represents a hydrogen atom or a C_{1-4}alkyl, C_{1-4}alkoxy, phenyl or amino group;

R^9 represents a hydrogen atom or a methyl group;

R^{10} represents a methyl, phenyl, amino or dimethylamino group;

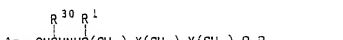
or P represents a pyridyl group optionally substituted by one or two substitutents selected from halogen atoms or hydroxy, C_{1-3}alkyl and C_{1-3}alkoxy groups.

The compounds have a stimulant action at β_2-adrenoreceptors and are useful, in particular, in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

CHEMICAL COMPOUNDS

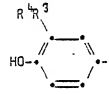
This invention relates to novel ethanolamine derivatives having a stimulant action at β_2-adrenoreceptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Thus the present invention provides compounds of the general formula (I)



(I)

and physiologically acceptable salts and solvents (e.g. hydrates) thereof wherein Ar represents

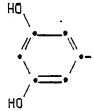
(a) 

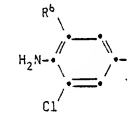
where

R^3 is a bond or a straight or branched C_{1-2} alkylene group,

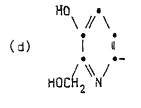
R^4 is a hydroxy group or a group R^5NH-where

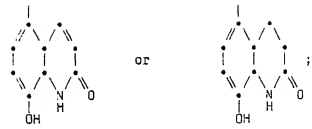
R^5 represents a group of CH_3SO_2-, HCO-or NH_2CO-,

(b) 

(c) 

where R^6 is a chlorine atom or the group F_3C-.





k represents an integer from 1 to 8,
m represents zero or an integer from 2 to 7 and
n represents an integer from 2 to 7 with the proviso that the sum total of k, m and n is 4 to 12;
R^1 and R^2 each represents a hydrogen atom or a methyl or ethyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 2;
R^{30} represents hydrogen or C_{1-2} alkyl;
X represents an oxygen or sulphur atom; and
Y an Q may each represent a bond or an oxygen or sulphur atom with the provisos that at least one of Y and Q represents an oxygen or sulphur atom and when Y is a bond m is zero, or when Y represents an oxygen or sulphur atom m is an integer from 2 to 7;
P represents a phenyl group optionally substituted by one or more substituents selected from halogen atoms, or the groups, C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, $-CH_2OH$, $-(CH_2)_2OH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2(CH_2)_{2}CH_3$, $-R^7$, COR^7, $-NHCOR^8$ or $-NR^9SO_2R^{10}$; where
R^7 represents an amino, aminoC_{1-3} alkyl, aminoC_{1-3}dialkyl, pyrrolidino, piperidino, hexamethylenimino, piperazino, N-methylpiperazino or morpholino group;
R^8 represents a hydrogen atom or a C_{1-4} alkyl, C_{1-4} alkoxy, phenyl or amino group;
R^9 represents a hydrogen atom or a methyl group;
R^{10} represents a methyl, phenyl, amino or dimethylamino group;
or P represents a pyridyl group optionally substituted by one or two substituents selected from halogen atoms or hydroxy, C_{1-3} alkyl or C_{1-3} alkoxy groups;

It will be appreciated that the compounds of general formula (I) possess one or more asymmetric carbon atoms, namely the carbon atom of the $-\underset{\underset{OH}{|}}{CH}-$ group and, when R^1 and R^2 are different groups or R^{30} is not hydrogen atom, the carbon atom(s) to which these are attached.

The compounds according to the invention thus include all enantiomers, diastereoisomers and mixtures thereof, including racemates. Compounds in which the carbon atom in the $-\underset{\underset{OH}{|}}{CH}-$ group is in the R configuration are preferred.

In the general formula (I), the chain $-(CH_2)_k-$ may be for example $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$ or $-(CH_2)_7-$. The chains $-(CH_2)_m-$ and $-(CH_2)_n-$ may be for example $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, or $-(CH_2)_6-$, or the chain $-(CH_2)_m-$ may be a bond.

In general, the total number of carbon atoms in the chains $-(CH_2)_k-$, $-(CH_2)_m$ and $-(CH_2)_n-$ is preferably 6 to 12 inclusive and may be for example 7,8,9 or 10. Compounds wherein the sum total of carbon atoms in the chains $-(CH_2)k-$,$-(CH_2)_m-$ and $-(CH_2)_n-$ is 7, 8 or 9 are particularly preferred.

In the compounds of formula (I) R^1 and R^2, for example, may each be methyl or ethyl groups except that if one of R^1 and R^2 is an ethyl group, the other is a hydrogen atom. R^1 and R^2 are each preferably a hydrogen atom or a methyl group.

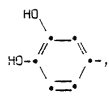
R^{30} in the compounds of formula (I) may represent for example a methyl or ethyl group or particularly a hydrogen atom.

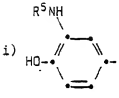
In the definition of Ar in compounds of formula (I), R^3 may be, for example, $-CH_2-$, $-\underset{\underset{CH_3}{|}}{CH}-$ or $-(CH_2)_2-$.

Ar in compounds of formula (I) may be for example

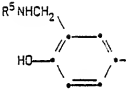
f) 

g) 

h) 

i) 

(where R^5 is HCO-, NH_2CO-, or CH_3SO_2-),

j) 

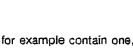
(where R^5 is as just defined), or a group of type b), c), d) or e).

Preferred compounds are those of formula (I) wherein Ar represents a group of type b), c), d), f), or i).

Particularly preferred compounds from within this group are compounds of formula (I) wherein Ar represents a group of type c), f) or i; where R^5 is CH_3SO_2-).

Especially preferred are compounds were Ar represents a group of type c; where R^6 is a chlorine atom) or a group of type f).

P may for example represent a phenyl group. Examples of the optional substituents which may be present on the phenyl group represented by P include bromine, iodine, chlorine, fluorine, methyl, ethyl, methoxy, ethoxy, amino, methylamino, ethylamino, dimethylamino diethylamino, morpholino, piperidino, piperazino, N-methylpiperazino, -NHCHO, -$NHCOR^8$ [where R^8 is C_{1-4} alkyl, (e.g. methyl, ethyl, isopropyl or n-butyl), C_{1-4} alkoxy (e.g. methoxy, ethoxy, isopropoxy or n-butoxy), phenyl or amino], -$NHSO_2CH_3$, -$NR^9SO_2R^{10}$, (where R^9 represents a hydrogen atom or a methyl group and R^{10} represents methyl, phenyl, amino or dimethylamino), -COOH, -$COOCH_3$, -$COO(CH_2)_2CH_3$, -$CON(CH_2CH_3)_2$, -$CONH_2$, -$CON(CH_3)_2$,



hydroxyl, -CH_2OH, or -$(CH_2)_2OH$.

The phenyl group represented by P may for example contain one, two or three substituents, which may be present at the 2-, 3-, 4-, 5-or 6-positions on the phenyl ring.

Preferred compounds are those of formula (I) wherein P represents an optionally substituted phenyl group containing one or two substituents selected from halogen (e.g. chlorine) atom(s), C_{1-5} alkyl (e.g. methyl) or C_{1-5} alkoxy (e.g. methoxy) groups or the groups -$NHCOCH_3$, -$CO_2(CH_2)_2CH_3$ or -$CON(CH_2CH_3)_2$.

P may also for example represent a pyridyl group. This may be attached to the rest of the molecule at either the 2-, 3-or 4-position.

When the pyridyl group is substituted, the substituents may be at the 2-, 3-, 4-, 5-or 6-position(s) in the ring. When the pyridyl group is substituted by one or two halogen atoms, these may be fluorine, chlorine or bromine. Preferably, when substituted, the pyridyl group is attached to the rest of the molecule at the 2-position and it contains a single substituent at the 3-, 5-or 6-position.

A preferred group of compounds are those of formula (I) in which P represents an optionally substituted

pyridyl group, and more especially a pyridyl group attached to the rest of the molecule at the 2-, 3-or 4-position, and optionally containing a single substituent selected from hydroxy, C_{1-3} alkyl (e.g. methyl), C_{1-3} alkoxy (e.g. methoxy) or halogen (e.g. bromine). Within this group particularly preferred compounds are those in which P is an unsubstituted pyridyl group.

In the general formula (I) X may represent an oxygen or sulphur atom and Y and Q may each represent a bond or an oxygen or sulphur atom.

A preferred group of compounds are those of formula (I) in which X is an oxygen atom. Also preferred are compounds of formula (I) where Y represents a bond or an oxygen or sulphur atom. Another group of preferred compounds are those of formula (I) where Q represents a bond or an oxygen or sulphur atom.

Preferred compounds from within this group are those wherein Y is a bond and Q is an oxygen or sulphur atom.

Additional preferred compounds are those of formula (I) where X is an oxygen atom, Y is a sulphur or more preferably an oxygen atom and Q is a bond. Another group of preferred compounds are those of formula (I) wherein X is an oxygen atom, Y is an oxygen atom and Q is an oxygen atom.

Preferred compounds according to the invention are
4-hydroxy-α'-[[[6-[(4-phenylthio)butoxy]hexyl]amino]methyl]-1,3-benzenedimethanol,
4-[3-[[6-[[2-(4-amino-3,5-dichlorophenyl)-2-hydroxyethyl]amino]hexyl]oxy]propyl]-N,N-diethylbenzamide,
4-hydroxy-α'-[[[3-[2-(4-phenylbutoxy)ethoxy]propyl]amino]methyl]-1, 3-benzenedimethanol,
4-amino-3,5-dichloro-α-[[[3-[2-(3-phenoxypropoxy)ethoxy]propyl]amino]methyl]benzenemethanol,
4-amino-3,5-dichloro-α-[[[3-[2-(3-phenylpropoxy)ethoxy]propyl]amino]methyl]benzenemethanol,
[4-amino-3,5-dichloro-α-[[[6-[2-[[2-(2-pyridinyl)ethyl]thio]ethoxy]hexyl]amino]methyl]benzenemethanol and their physiologically acceptable salts and solvates.

A further preferred compound according to the invention is 4-hydroxy-α'-[[[3-[2-[3-(4-acetamido)-phenylpropoxy]ethoxy]propyl]amino]methyl]-1,3-benzenedimethanol.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, maleates, tartrates, citrates, benzoates, 4-methoxybenzoates, 2-or 4-hydroxybenzoates, 4-chlorobenzoates, benzenesulphonates, p-toluenesulphonates, naphthalenesulphonates, methanesulphonates, sulphamates, ascorbates, salicylates, acetates, diphenylacetates, triphenylacetates, adipates, fumarates, succinates, lactates, glutarates, gluconates, tricarballylates, hydroxy-naphthalenecarboxylates (e.g. 1-hydroxy-or 3-hydroxy-2-naphthalenecarboxylates including 4,4'-methylenebis-(3-hydroxy-2-naphthalenecarboxylic acid), or oleates. The compounds may also form salts with suitable bases. Examples of such salts include alkali metal (e.g. sodium and potassium), and alkaline earth metal (e.g. calcium or magnesium) salts.

The compounds according to the invention have a stimulant action at β_2-adrenoreceptors, which furthermore is of a particularly advantageous profile. The stimulant action was demonstrated in the isolated trachea of the guinea-pig, where compounds were shown to cause relaxation of contractions induced by PGF $_{4}$ or electrical stimulation. Compounds according to the invention have shown a particular desirable duration of action in these tests.

The compounds according to the invention may be used in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

The compounds according to the invention are also indicated as useful for the treatment of inflammatory and allergic skin diseases, congestive heart failure, depression, premature labour, glaucoma and in the treatment of conditions in which there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

The invention accordingly further provides compounds of formula (I) and their physiologically acceptable salts and solvates for use in the therapy or prophylaxis of diseases associated with reversible airwars obstruction in human or animal subjects.

The compounds according to the invention may be formulated for administration in any convenient way. The invention therefore includes within its scope pharmaceutical compositions comprising at least one compound of formula (I) or a physiologically acceptable salt or solvate thereof formulated for use in human or veterinary medicine. Such compositions may be presented for use with physiologically acceptable carriers or excipients, optionally with supplementary medicinal agents.

The compounds may be formulated in a form suitable for administration by inhalation or insufflation, or for oral, buccal, parenteral, topical (including nasal) or rectal administration. Administration by inhalation or insufflation is preferred.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation form pressurised packs, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suit-

able gas, or from a nebuliser. In the case of pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in for example capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powder, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For buccal administration the composition may take the form of tablets, drops or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form in ampouls, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in the powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For topical administration and pharmaceutical composition may take the form of ointments, lotions or creams formulated in a conventional manner, with for example an aqueous or oily base, generally with the addition of suitable thickening agents and/or solvents. For nasal application, the composition may take the form of a spray, formulated for example as an aqueous solution or suspension or as an aerosol with the use of a suitable propellant.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

Where pharmaceutical compositions are described above for oral, buccal, rectal or topical administration, these may be presented in a conventional manner associated with controlled release forms.

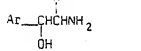
A proposed daily dosage of active compound for the treatment of man is 0.005mg to 100mg, which may be conveniently administered in one or two doses. The precise dose employed will of course depend on the age and condition of the patient and on the route of administration. Thus a suitable dose for administration by inhalation is 0.005mg to 20mg, for oral administration is 0.02mg to 100mg, and for parenteral administration is 0.01mg to 2mg for administration by bolus injection and 0.01mg to 25mg for administration by infusion.

In the following description relating to the preparation of compounds of formula (I) and intermedfates used in the preparation thereof, k, m, n, Ar, R^1, R^2, R^{30} X, Y, P and Q are as defined for general formula (I) unless otherwise specified. Any hydroxy and/or amino groups present in the starting materials may need to be in a protected form and the final step may be the removal of a protecting group. Suitable protecting groups and methods for their removal are for example those described in "Protective Groups in Organic Chemistry", by Theodora Greene (John Wiley and Sons Inc. 1981). Thus hydroxy groups may for example be protected by arylmethyl groups such as benzyl, diphenylmethyl or triphenylmethyl, or as tetrahyropyranyl derivatives. Suitable amino protecting groups include arylmethyl groups such as benzyl, α-methylbenzyl, diphenylmethyl or triphenylmethyl, and acyl groups such as acetyl, trichloroacetyl or trifluoroacetyl. Conventional methods of deprotection may be used. Thus for example arylmethyl groups may be removed by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal). Tetrahydropyranyl groups may be cleaved by hydrolysis under acidic conditions. Acyl groups may be removed by hydrolysis with a base such as sodium hydroxide or potassium carbonate, or a group such as trichloroacetyl may be removed by reduction with, for example, zinc and acetic acid.

The compounds according to the invention may be prepared by a number of processes.

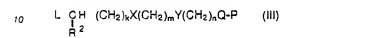
In one general process (1), a compound of general formula (I) may be prepared by alkylation, using conventional alkylation procedures.

Thus, for example in one process (a), a compound of general formula (I) in which R^1 is a hydrogen atom may be prepared by alkylation of an amine of general formula (II)



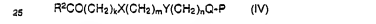
followed where necessary by removal of any protecting groups.

The alkylation (a) may be effected using an alkylating agent of general formula (III):



(wherein L represents a leaving group, for example a halogen atom such as chlorine, bromine or iodine, or a hydrocarbylsulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonyloxy). The alkylation is preferably effected in the presence of a suitable acid scavenger, for example, inorganic bases such as sodium or potassium carbonate, organic bases such as triethylamine, N,N-diisopropylethylamine or pyridine, or alkylene oxides such as ethylene oxide or propylene oxide. The reaction is conveniently effected in a solvent such as acetonitrile or an ether e.g. tetrahydrofuran or dioxan, a ketone e.g. butanone or methyl isobutyl ketone, a substituted amide e.g. dimethylformamide or a chlorinated hydrocarbon e.g. chloroform at a temperature between ambient and the reflux tempelature of the solvent.

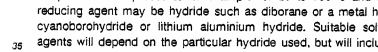
According to another example (b) of an alkylation process, a compound of general formula (I) in which R^1 represents a hydrogen atom may be prepared by alkylation of an amine of general formula (II) with a compound of general formula (IV):



in the presence of a reducing agent, following where necessary by removal of any protecting groups.

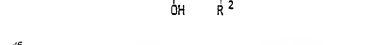
Suitable reducing agents include hydrogen in the presence of a catalyst such as platinum, platinum oxide, palladium, palladium oxide, Raney nickel or rhodium, on a support such as charcoal, using an alcohol, e.g. ethanol or an ester e.g. ethyl acetate or an ether e.g. tetrahydrofuan, or water, as reaction solvent, or a mixture of solvents, e.g. a mixture of two or more of those just described at normal or elevated temperature and pressure, for example for 20 to 100°C and from 1 to 10 atmospheres. Alternatively the reducing agent may be hydride such as diborane or a metal hydride such as sodium borohydride, sodium cyanoborohydride or lithium aluminium hydride. Suitable solvents for the reaction with these reducing agents will depend on the particular hydride used, but will include alcohols such as methanol or ethanol, or ethers such as diethyl ether or tert-butyl methyl ether, or tetrahydrofuran.

Alkylation of an amine (II) with a compound of formula (IV) may result in formation of the intermediate imine of formula (V)



Reduction of the imine using the conditions described above, gives a compound of general formula (I).

In another general process (2), a compound of general formula (I) may be prepared by reduction. Thus, for example, a compound of general formula (I) may be prepared by reducing an intermediate of general formula (VI):



(wherein X^1 represents a reducible group and R^{11} represents a hydrogen atom or a protecting group) followed where necessary by removal of any protecting groups. Suitable reducible groups include those wherein X^1 is a group >C=O, and the reduction may for example be effected using reducing agents

conveniently employed for the reducing of ketones. Thus when X' in general formula (VI) represents a >C=O group this may be reduced to a -CH(OH)-group using, for example, a hydride such as diborane or a metal hydride such as lithium aluminium hydride, sodium bis(2-methoxyethoxy) aluminium hydride, sodium borohydride or aluminium hydride. The reaction may be effected in a solvent, where appropriate an alcohol e.g. methanol or ethanol, or an ether e.g. diethyl ether or tetrahydrofuran, or a halogenated hydrocarbon e.g. dichloromethane, at a temperature of 0°C to the reflux temperature of the solvent. Alternatively, reduction may be effected using hydrogen in the presence of a catalyst as previously described for process (1) part (b).

In one convenient aspect of the reduction process, R^{11} may be a protecting group which is capable of being removed under the reducing conditions used, for example hydrogen and a catalyst, thus avoiding the need for a separate deprotection step. Suitable protecting groups include arylmethyl groups such as benzyl, benzhydryl and α-methylbenzyl.

In the general processes described above, the compound of formula (I) obtained may be in the form of a salt, conveniently in the form of a physiologically acceptable salt. Where desired, such salts may be converted to the corresponding free bases using conventional methods. Physiologically acceptable salts of the compounds of general formula (I) may be prepared by reacting a compound of general formula (I) with an appropriate acid or base in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol, e.g. methanol, ethanol or iso-propanol.

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of general formula (I), using conventional methods.

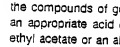
When a specific enantiomer of a compound of general formula (I) is required, this may be obtained by resolution of a corresponding racemate of a compound of general formula (I) using conventional methods.

Thus, in one example an appropriate optically active acid may be used to form salts with the racemate of a compound of general formula (I). The resulting mixture of isomeric salts may be separated for example by fractional crystallisation, into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

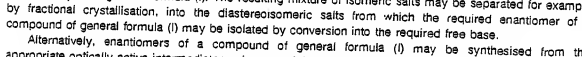
Specific diastereoisomers of a compound of formula (I) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or by conversion of a mixture of isomers of a compound of general formula (I) into appropriate diastereoisomeric derivatives e.g. salts which then can be separated by conventional means e.g. by fractional crystallisation.

The intermediate compounds of general formula (VI) in which X' represents a group >C=O may be prepared from a haloketone of formula (VII):



Ar-CO $\underset{R^{30}}{\overset{|}{C}}$H Hal (VII)

(where Hal represents a halogen atom, and any hydroxyl and/or amino group(s) in the group Ar may optionally be protected) by reaction with an amine of general formula (VIII)



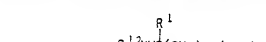
$R^{12}NH\underset{R^{2}}{\overset{R^{1}}{\overset{|}{\underset{|}{C}}}}(CH_2)_kX(CH_2)_mY(CH_2)_nQ-P$ (VIII)

(wherein R^{12} is a hydrogen atom or a group convertible thereto by catalytic hydrogenation).

The reaction may be effected in a cold or hot solvent, for example dimethylformamide, tetrahydrofuran, a halogenated hydrocarbon such as dichloromethane, or an ester such as ethyl acetate, in the presence of a base such as diisopropylethylamine.

The amines of formula (II) and haloketones for formula (VII) are either known compounds or may be prepared by methods analogous to those used for the preparation of the known compounds.

Intermediates of formula (III) may be prepared from the corresponding alcohols of formula (IX) using methods capable of effecting the conversion.



HO-$\underset{R^{2}}{\overset{|}{C}}$H $(CH_2)_kX(CH_2)_mY(CH_2)_nQ-P$ (IX)

For example compounds of formula (III) where L represents a halogen atom may be prepared by reaction of the compounds of formula (IX) with a halogenating agent such as triphenylphosphine-tetrahalogenomethane adduct (conveniently formed in situ e.g. by the reaction of triphenylphosphine and carbontetrabromide). The reaction may take place in the presence of a solvent such as a chlorinated hydrocarbon (e.g. dichloromethane) at a temperature range of 0-30°.

Alcohols of formula (IX) may be prepared by reacting a compound of formula (X)

$$L\text{-}(CH_2)_mY(CH_2)_nQ\text{-}P \qquad (X)$$

(where L is as defined above) with a compound of formula (XI)

$$HO\text{-}\underset{\underset{R^2}{|}}{C}H\text{-}(CH_2)_k\text{-}XH \qquad (XI)$$

The reaction may take place optionally in a solvent such as ether (e.g. tetrahydrofuran or 1, 2-dimethoxyethane), an alcohol (e.g. methanol) or an amide (e.g. dimethylformamide) at a temperature up to the boiling point of the solvent. The reaction may be effected by first generating the anion of the compound of general formula (XI) by adding for example sodium, sodium hydride, potassium hydroxide or sodium hydroxide.

Compounds of formula (X) may be prepared from the corresponding compounds of formula (XII)

$$HO\text{-}(CH_2)_mY(CH_2)_nQ\text{-}P \qquad (XII)$$

using methods capable of effecting the conversion. For example when L in general formula (X) represents a hydrocarbylsulphonyloxy group (e.g. methanesulphonyloxy) such compounds may be prepared by reacting the compound of formula (XII) with methanesulphonyl chloride in the presence of a base (e.g. triethylamine). The reaction conveniently takes place in the presence of a solvent such as halogenated hydrocarbon (e.g. dichloromethane) at a temperature ranging from 0.25°.

Compounds of formula (XII) may be prepared by reacting a compound of formula (XIII) with a compound of formula (XIV)

$$L\text{-}(CH_2)_nQ\text{-}P$$
$$HO(CH_2)_mYH \qquad (XIV)$$

under conditions as described for the preparation of compounds of formula (IX) above.

Compounds of formula (XIII) are either known compounds or may be prepared from the corresponding alcohols as described for the preparation of compounds of formula (III) above.

Compounds of formulae (XI) and (XIV) are either known compounds or may be prepared by methods analagous to those used for the preparation of known compounds.

In addition, intermediates of formulae (III), (IV), (VIII), (X), (XII), and (XIII) may be prepared by methods analogous to those used for the preparation of known compounds. Suitable methods include those described in UK Patent Specifications Nos. 2140800A and 2159151A and in the exemplification included hereinafter.

The following examples illustrate the invention. Temperatures are in °C. 'Dried' refers to drying using magnesium sulphate or sodium sulphate. Unless otherwise stated, thin layer chromatography (t.l.c.) was carried out on silica, and flash column chromatography (FCC) was carried out on silica (Merck 9385), using one of the following solvent systems : A - ethyl acetate:cyclohexane; B -diethyl ether:cyclohexane; C - light petroleum (b.p. 40-60°): diethyl ether: D - ethyl acetate:methanol:triethylamine: E-toluene:ethanol: 0.88 ammonia; F-hexane: diethyl ether; G-toluene: ethanol: triethylamine; H-toluene: ethylacetate: triethylamine. The following abbreviations are used: DMF - dimethylformamide; THF -tetrahydrofuran; DMSO - dimethylsulphoxide; PE - light petroleum (b.p. 40-60°); TAB - tetra-n-butylammonium hydrogen sulphate; DEA -N,N-diisopropylethylamine.

Intermediate 1

is α'-(aminomethyl)-4-hydroxy-1,3-benzenedimethanol.

Intermediate 2

[4-[(6-Bromohexyl)oxy]butoxy]benzene

4-Phenoxy-1-butanol (4g), 1,6-dibromohexane (6.7ml), TAB (0.8g) and sodium hydroxide (9.4g in 18ml water) were stirred at room temperature under nitrogen for 20h. Water (80ml) was added and the mixture extracted with diethyl ether (3x100ml). The combined organic extracts were washed with water (50ml), brine (50ml), dried and evaporated to give a colourless liquid. This was applied to an FCC column and eluted with cyclohexane (2l) and then with System A (1:40). The resulting oil was distilled to give the title compound (3.4g) as a colourless oil b.p. 150°/3.5 mmHg T.l.c. (System A 1:6) Rf 0.3.

Intermediate 3

[[3-[(6-Bromohexyl)oxy]propyl]thio]benzene

3-(Phenylthio)-1-propanol (3.00g), 1,6-dibromohexane (5.5ml), aqueous 12.5M sodium hydroxide (27ml) and TAB (802mg) were vigorously stirred at room temperature overnight. The mixture was diluted with water (60ml), extracted with diethyl ether (3x90ml), and the combined, dried organic extracts were evaporated. The residual oil was purified by FCC eluting with System B (1:99→1:24) to give the title compound (4.01g) as a colourless oil. T.l.c. (System B 1:3) Rf 0.35.

Intermediate 4

[2-[(6-Bromohexyl)oxy]ethoxy]benzene

2-Phenoxyethanol (2.76g), 1,6-dibromohexane (14.6g), TAB (1g) and 50% sodium hydroxide (20m.t.) were vigorously stirred for 21h, added to water (100m.t.) and extracted with diethyl ether (3x100m.t.). The dried extract was evaporated and the residual colourless liquid (15g) was purified by FCC eluting with cyclohexane followed by System A (1:1). Evaporation of the latter eluate gave the title compound (5.0g) as a colourless liquid. T.l.c. (System A 1:1) Rf 0.6.

Intermediate 5

[[4-[(6-Bromohexyl)oxy]butyl]thio]benzene

4-(Phenylthio)-1-butanol (5.25g), 1,6-dibromohexane (21.08g), TAB (1g) and 40% sodiumhydroxide solution (45m.t.) were stirred together at room temperature for 18h. The mixture was diluted with water (150m.t.), extracted with diethyl ether (2x150m.t.), the organic layer washed with brine (100m.t.), dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System A (0:20 → 1:19) gave the title compound (5.54g) as a colourless oil. T.l.c. (System A 1:9) Rf 0.12.

Intermediate 6

3-(4-Methoxyphenoxy)-1-propanol

To a solution of 4-methoxyphenol (1.24g) and 3-bromopropanol (1.18m ℓ) in DMSO (15m ℓ) was added in one portion powdered sodium hydroxide (1.12g). The mixture was stirred for 0.75h then poured into 2N hydrochloric acid (100m ℓ) and extracted with ethyl acetate (100m ℓ). The organic phase was washed with water (100m ℓ), dried and concentrated to give the title compound (1.785g) as a pale brown solid, m.p. 56-60°.

Intermediate 7

1-[3-[(4-Bromobutyl)oxy]propoxy]-4-methoxybenzene

A mixture of Intermediate 6 (16.43g), dibromobutane (42.9m ℓ), TAB (3.05g), and 50% w/v sodium hydroxide solution (144m ℓ) was stirred at 20° for 20h. Diethyl ether (400m ℓ) was added and the mixture washed with water (3x400m ℓ), dried and evaporated. The excess of dibromide was removed at 70° under high vacuum and the oily residue (~40g) purified by FCC eluting with System C (8:1). The title compound - (19.97g) was obtained as a colourless oil. T.l.c (System C 8:1) Rf 0.14.

Intermediate 8

6-[3-[4-(Methoxy)phenoxy]propoxy]-2-hexanone

A mixture of Intermediate 7 (1.268g) and magnesium (100mg) in dry diethyl ether (15m ℓ) containing a little iodine was heated under reflux for 2 h. This mixture was then cooled in an ice bath and treated with a solution of dimethylacetamide (0.37m ℓ) in diethyl ether (10m ℓ). After 1h at 20° 3N hydrochloric acid (50m ℓ) was added and stirring continued at 20° for a further 0.5h. The layers were separated and the organic phase was washed with 8% sodium bicarbonate solution (50m ℓ), dried and evaporated to give a white semi-solid. FCC eluting with System C (3:2 then 1:1) gave the title compound (284mg) as a pale yellow oil. T.l.c. (System C 1:1) Rf 0.25.

Intermediate 9

3-(4-Bromophenoxy)-1-propanol

Powdered sodium hydroxide (2.2g) was added to a solution of 4-bromophenol (3.46g) and 3-bromopropanol (2.36m ℓ) in DMSO (18m ℓ). The mixture was stirred vigorously at 20° for 2.5h then diluted with ethyl acetate (100m ℓ) and washed successively with 2N hydrochloric acid (100m ℓ), water (100m ℓ x 2) and brine. Concentration of the dried organic phase yielded the title compound (5.02g) as a pale orange oil. T.l.c. (diethyl ether) Rf 0.32.

Intermediate 10

1-Bromo-4-[3-[(6-bromohexyl)oxy]propoxy]benzene

A mixture of Intermediate 9 (4.48g), 1,6-dibromohexane (11.9mℓ), TAB (659mg) and 50% aqueous sodium hydroxide solution (31mℓ) was stirred vigorously at 21° for 19h. Diethyl ether (200mℓ) was added and the mixture was washed with water (2x200mℓ), dried and evaporated. The excess of dibromide was removed at 70°/1mm Hg and the residue purified by FCC eluting with System C (8:1). The title compound - (5.37g) was obtained as a pale yellow oil. T.l.c. (System C 8:1) Rf 0.20.

Intermediate 11

4-[3-[(6-Bromohexyl)oxy]propoxy]benzoic acid

A solution of Intermediate 10 (1.97g) in THF (20mℓ) was cooled to -70° under nitrogen and treated with n-butyl lithium in hexane (1.6M; 3.44mℓ). After 0.5h powdered solid carbon dioxide (~ 8g) was added and the mixture allowed to warm to 20° over 1h. THF was removed in vacuo and the residue diluted with water (150mℓ), basified with 2N sodium hydroxide solution and washed with diethyl ether (100mℓ). The aqueous phase was then acidified with 2N hydrochloric acid and extracted with diethyl ether (2x100mℓ). Evaporation of these combined, dried extracts gave a white solid which was triturated with PE (2x10mℓ) to yield the title compound (1.26g) as a white powder, m.p. 72-75°.

Intermediate 12

Propyl 4-[3-[(6-bromohexyl)oxy]propoxy]benzoate

A mixture of Intermediate 11 (1.0g), ethereal hydrogen chloride (1mℓ) and n-propanol (5mℓ) was heated at ca 70° for 4h. The pale brown solution was diluted with diethyl ether (50mℓ), washed with 8% sodium bicarbonate solution (2x50mℓ), dried and evaporated. The residual oil (1.05g) was purified by FCC eluting with System C (2:1). The title compound (886mg) was obtained as a colourless oil. T.l.c. (System C 1:1) Rf 0.48.

Intermediate 13

1-[[[3-[(6-Bromohexyl)oxy]]propyl]thio]-4-methylbenzene

3-[(4-Methylphenyl)thio]-1-propanol (4.0g), 1,6-dibromohexane (16.06g), 40% sodium hydroxide solution (40mℓ) and TAB (1g) were stirred together at room temperature for 18h. The mixture was diluted with water (150mℓ), extracted with ethyl acetate (2x150mℓ), which was dried and evaporated in vacuo to give a colourless oil. Purification by FCC eluting with System A (0:20→1:19) gave the title compound (5.0g) as a colourless oil. T.l.c. (System A 1:9) Rf 0.53.

Intermediate 14

2-[(6-Bromohexyl)oxy]ethoxy]-3,4-dimethylbenzene

2-(3,4-Dimethylphenoxy)ethanol (8.3g), 1,6-dibromohexane (36.6g), TAB (2g) and 50% sodium hydroxide solution (50mℓ) were vigorously stirred together for 17h. The emulsion was added to water (150mℓ) and extracted with diethyl ether (3x50mℓ). The dried ethereal solution was evaporated to a colourless liquid (40.3g) which was purified by FCC eluting with cyclohexane followed by System A (1:1) to yield the title compound (4.7g) as a semi-solid. T.l.c. (System A 1:1) Rf 0.5.

Intermediate 15

[2-[(5-Bromopentyl)oxy]ethyl]thio]-4-chlorobenzene

2[(4-Chlorophenyl)thio]ethanol (3.8g), 1,5-dibromopentane (13.8), TAB (1g) and 50% aqueous sodium hydroxide (20mℓ) were stirred together for 17h and extracted with diethyl ether (3x50mℓ) and water (50mℓ). The dried ethereal solution was evaporated and the residual colourless oil (15.0g) was purified by FCC eluting with cyclohexane, followed by System A (1:1) to give the title compound (3.0g). T.l.c. (System a 1:1) Rf 0.7.

Intermediate 16

3-(4-Bromophenoxy)-1-propanol

Powdered sodium hydroxide (2.2g) was added to a solution of 4-bromophenol (3.46g) and 3-bromopropanol (2.36mℓ) in DMSO (18mℓ). The mixture was stirred vigorously at 20° for 2.5h then diluted with ethyl acetate (100mℓ) and washed with 2N hydrochloric acid (100mℓ), water (100mℓ x 2) and brine. Concentration of the dried organic phase yielded the title compound (5.02g) as a pale orange oil. T.l.c. (diethyl ether) Rf 0.32.

Intermediate 17

1-Bromo-4-[3-[(6-bromohexyl)oxy]propoxy]benzene

A mixture of Intermediate 16 (4.48g), 1,6-dibromohexane (11.94mℓ), TAB (659mg), and 50% aqueous sodium hydroxide solution (31mℓ) was stirred vigorously at 21° for 19h. Diethyl ether (200mℓ) was added and the mixture washed with water (2x200mℓ), dried and evaporated. The excess of dibromide was removed at 70°/1mm Hg and the residue purified by FCC eluting with System C (8:1), to give the title compound (5.37g) as a pale yellow oil. T.l.c. (System C 8:1) Rf 0.52.

Intermediate 18

4-[3-[(6-Bromohexyl)oxy]propoxy]benzoic acid

A solution of Intermediate 17 (1.97g) in THF (20mℓ) was cooled to -70° under nitrogen and treated with n-butyl lithium in hexane (1.6M; 3.44mℓ). After 0.5h powdered solid carbon dioxide (~ 8g) was added and the mixture allowed to warm to 20° over 1h. THF was removed in vacuo and the residue diluted with water

(150mℓ), basified with 2N sodium hydroxide solution and washed with diethyl ether (100mℓ). The aqueous phase was then acidified with 2N hydrochloric acid and extracted with diethyl ether (2x100mℓ). Evaporation of the combined dried extracts gave a white solid which was triturated with PE to yield the title compound - (1.26g) as a white powder, m.p. 72-75°.

Intermediate 19

4-[3-[(6-Bromohexyl)oxy]propoxy]benzoyl chloride

Intermediate 18 (5.0g) in thionyl chloride (8mℓ) was refluxed under nitrogen for 2h. The solution was evaporated to give an oil and toluene was added. The solution was evaporated to give the title compound - (5.37g) as an orange oil. T.l.c. (System F 1:1) Rf 0.38.

Intermediate 20

[3-[(6-Bromohexyl)oxy]propoxy]-N,N-diethylbenzamide

Intermediate 19 (5.17g) was added dropwise to diethylamine (1.1g) in triethylamine (15mℓ) with water-bath cooling. The reaction mixture was stirred at room temperature under nitrogen for 3h and diluted with diethyl ether (50mℓ). The solid was collected by filtration and the filtrate was concentrated to give an oil which was purified by FCC eluting with System F (4:3) to give the title compound (4.87g) as a pale yellow oil. T.l.c. (System F 1:1)) Rf 0.13.

Intermediate 21

N,N-Diethyl-4-[3-[[6-[(phenylmethyl)amino]oxy) propoxy]benzamide

Intermediate 20 (2.22g) was added dropwise to benzylamine (8.0mℓ) at 140° under nitrogen. The solution was stirred at 140° for 1h, cooled, and partitioned between ethyl acetate (100mℓ) and 8% aqueous sodium bicarbonate (70mℓ). The dried organic layer was concentrated and benzylamine was distilled off (Kugelrohr) under vacuum. The residue was purified by FCC eluting with ethyl acetate-triethylamine (100:1) to give the title compound (1.80g) as a pale yellow oil. T.l.c. (Ethyl acetate + few drops triethylamine) Rf 0.22.

Intermediate 22

4-[3-[[6-[[2-(4-Amino-3,5-dichlorophenyl)-2-hydroxyethyl](phenylmethyl)amino)hexyl]oxy]propoxy]-N,N-diethylbenzamide

A solution of 1-(4-amino-3,5-dichlorophenyl)-2-bromoethanone (1.08g), Intermediate 21 (1.88g) and DEA (0.49g) in THF (15mℓ) was left to stand for 16h at room temperature under nitrogen. The reaction mixture was filtered and the filtrate was concentrated to give an oil which in methanol (20mℓ) was ice-cooled and treated portionwise with sodium borohydride (0.54g). The reaction mixture was stirred at room temperature

under nitrogen for 2h and the solvent was evaporated. Water (70m t) was added to the residue and extracted with ethyl acetate (3x50m t). The combined extracts were washed with water (50m t) and brine (50m t), dried and concentrated to give an oil which was purified by FCC eluting with System G (97:3:1) to give the title compound (1.53g) as a yellow oil. T.l.c. (System G 95:5:1)) Rf 0.25.

Intermediate 23

3-Phenoxy-1-propanol methanesulphonate

Methanesulphonyl chloride (16.15g) was added dropwise to a stirred solution of 3-phenoxy-1-propanol (17.81g) and triethylamine (23.79g) in dry dichloromethane (120m t) at 0°C under nitrogen. The mixture was stirred at room temperature for 1h and then washed successively with 2N hydrochloric acid (100m t), water (100m t), 8% sodium bicarbonate solution (100m t) and brine (100m t). The solution was dried and evaporated in vacuo to give an oil which solidified on standing to give the title compound (25.88g) as a waxy solid. T.l.c. (diethyl ether) Rf 0.50

Intermediate 24

2-(3-Phenoxypropoxy)ethanol

Sodium (2.80g) was dissolved in 1,2-ethanediol (22.00g) at ca 100° under nitrogen and 3-phenoxy-1-propanol methanesulphonate (25.5g) in 1,2-dimethoxyethane (50m t) was added dropwise at 100° under nitrogen. The mixture was stirred at 150° for 2h and then carefully diluted with water (150m t) and extracted with diethyl ether (2x150m t). The combined organic extracts were washed with water (2x150m t), dried and evaporated in vacuo to give the title compound (21.45g) as an oil. T.l.c. System B (1:1) Rf 0.13

In a similar manner to that described for Intermediate 23 and Intermediate 24 above, the following compounds were prepared:-

Intermediate 25

2-(3-Phenoxypropoxy)ethanol methanesulphonate (3.23g) as an oil (purification by FCC eluting with System F(1:1)) was obtained from Intermediate 24 (5.0g). T.l.c. (System F 1:1) Rf 0.10;

Intermediate 26

3-[2-(3-Phenoxypropoxy)ethoxy]-1-propanol (1.65g) (purification by FCC eluting with diethyl ether) was obtained from Intermediate 25 (3.1g) and 1,3-propanediol (2.84g). T.l.c. (diethyl ether) Rf 0.22;

Intermediate 27

2-(3-Phenylpropoxy)ethanol methanesulphonate (23.19g) as an oil was obtained from 2-(3-phenylpropoxy)ethanol (18.02g). T.l.c. (diethyl ether) Rf 0.5

Intermediate 28

3-[2-(3-Phenylpropoxy)ethoxy]-1-propanol (9.30g) (purification by FCC eluting with System B (2:3→1:1)) was obtained from Intermediate 27 (22.2g) and 1,3-propanediol (21.68g). T.l.c. (System B 1:1) Rf 0.2

Intermediate 29

2-(4-Phenylbutoxy)ethanol

Sodium (2.3g) was dissolved in ethane-1,2-diol (18.6g) under nitrogen benzenebutanol methanesulphonate (22.0g) was added dropwise at ca 50°. The mixture was heated at 80-100° for 2h to give a heavy precipitate. THF (50m*t*) was added and the resulting suspension was heated under reflux for 2h and then treated with water (50m*t*) before evaporating off the THF and extracting the residue with diethyl ether (2x100m*t*). The dried extract was evaporated and the residue was distilled to give the title compound - (12.5g) as a colourless oil b.p. 110-115°0.2mmHg (Kugelrohr).

Intermediate 30

2-(4-Phenylbutoxy)ethanol methanesulphonate

Methanesulphonyl chloride (7.5g) was added dropwise to Intermediate 29 (12.0g) and triethylamine (13.1g) in dichloromethane (75m*t*) at 0° under nitrogen. The resulting suspension was stirred at room temperature for 20 min and washed with hydrochloric acid (2M; 50m*t*), water (25m*t*), aqueous sodium bicarbonate (1M; 50m*t*), and brine (50m*t*). The dried organic phase was evaporated to give the title compound (15.7g) as an oil. T.l.c. (diethyl ether) Rf 0.5

Intermediate 31

3-[2-(4-Phenylbutoxy)ethyoxy]-1-propanol

Sodium (0.92g) was dissolved in propane-1,3-diol (9.0g) under nitrogen and Intermediate 30 (10.0g) was added dropwise at ca 65°. The resulting mixture was heated at ca 100° for 2h to produce a heavy precipitate. THF (50m*t*) was added and the mixture was heated under reflux for 3h, treated with water (50m*t*) and THF was removed under reduced pressure. The residue was extracted with diethyl ether (2x100m*t*) and the dried organic extract evaporated to give an oil, which was purified by FCC eluting with System B (2:3) to give the title compound (5.2g) as a colourless oil. T.l.c. (diethyl ether) Rf 0.35.

Intermediate 32

[3-[2-(3-Bromopropoxy)ethoxy]propoxy]benzene

Triphenylphospine (2.01g) in dry dichloromethane (16m*t*) was added dropwise over 20 min to a stirred solution of 3-[2-(3-phenoxypropoxy)ethoxy]-1-propanol (1.5g), and carbon tetrabromide (2.54g) in dry dichloromethane (27m*t*) at 0°C under nitrogen. The solution was allowed to warm to room temperature and stirred under nitrogen for 4h. The solution was purified by FCC eluting with System F (4:1) to give the title compound (1.75g) as a colourless oil. T.l.c. (System F 1:1) Rf 0.55

Intermediate 33

[3-[2(3-Bromopropoxy)ethoxy]propyl]benzene

Triphenylphosphine (12.59g), in dry dichloromethane was added dropwise over 20 min to a stirred solution of 3-[2-(3-phenylpropoxy)ethoxy]-1-propanol (8.8g) and carbon tetrabromide (15.92g) in dry dichloromethane (170m*t*) at 0°C under nitrogen. The solution was allowed to warm to room temperature and stirred under nitrogen for 30 min. The solution was concentrated to ca 30m*t* and then purified by FCC eluting with System B (0:10 → 2:3) to give the title compound (9.94g) as an oil. T.l.c. (System B 1:1) Rf 0.50

Intermediate 34

[4-[2-(3-Bromopropoxy)ethoxy]butyl]benzene

Triphenylphosphine (6.55g) in dichloromethane (30m*t*) was added dropwise to 3-[2-(4-phenylbutoxy)-ethoxy]-1-propanol (5.0g) and carbon tetrabromide (8.3g) in dichloromethane (30m*t*) at 0°. The mixture was stirred at room temperature for 1h, evaporated onto silica, and purified by FCC eluting with cyclohexane - followed by System B (1:9) to give the title compound (5.4g) as an oil. T.l.c. (System B 1:9) Rf 0.35

Intermediate 35

N-[3-[2-(3-Phenoxypropoxy)ethoxy]propyl]benzenemethanamine

[3-[2-(3-Bromopropoxy)ethoxy]propoxy]benzene (1.8g) was added dropwise with stirring to benzylamine (2.70g) at 130° under nitrogen. The solution was stirred at 130° under nitrogen for 2h, cooled and diluted with ethyl acetate (150m*t*), and washed with 2N hydrochloric acid (100m*t*). The aqueous phase was re-extracted with ethyl acetate (2x100m*t*) and the combinded organic phases washed with 8% sodium bicarbonate solution (150m*t*), dried and evaporated in vacuo to give the title compound (1.21g) as an oil. T.l.c. (System E 40:10:1) Rf 0.52

Intermediate 36

N-[3-[2-(3-Phenylpropoxy)ethoxy]propyl]benzenemethanamine

[3-[2-(3-Bromopropoxy)ethoxy]propyl]benzene (3.01g) was added dropwise over 5 min to benzylamine (5.35g) at 120° under nitrogen. The solution was stirred at 130° for 4.5h, cooled, diluted with ethyl acetate (200m*t*) and washed with 2N hydrochloric acid (150m*t*). The aqueous phase was re-extracted with ethyl acetate (2x100m*t*) and the combined organic phases washed with 8% sodium bicarbonate solution (200m*t*), dried and evaporated in vacuo to give the title compound (2.58g) as an oil. T.l.c. (System E 40:10:1) Rf 0.49

Intermediate 37

Methyl [(3-pyridinyl)oxy]acetate

Sodium hydride (3.78g, 80% suspension in oil) was added to a solution of 3-pyridinol (10g) in THF (150m*t*) at 0°. The mixture was stirred under nitrogen for 30min, treated dropwise with methyl

bromoacetate (19.3g), heated under reflux for 24h, poured into ice-water (200mℓ) and extracted with ethyl acetate (2 x 100mℓ). The combined organic extracts were dried and concentrated to give an oil which was purified by FCC, eluting with System G (98:2:1) to give the title compound (4g,) as an oil. T.l.c. (System E 80:20:1) Rf 0.46

Intermediate 38

2-[(3-pyridinyl)oxy]ethanol

Methyl [(3-pyridinyl)oxy]acetate (3.6g) in diethyl ether (80mℓ) was added dropwise to a stirred suspension of lithium aluminium hydride (826mg) in diethyl ether (100mℓ) at 0°. The mixture was stirred overnight at room temperature under nitrogen, water (1mℓ) was added, followed by 2N sodium hydroxide (1mℓ) amd water (3mℓ). The suspension was filtered and washed with ethyl acetate (3 x 100mℓ) then dichloromethane (300mℓ). The combined organic extracts were dried and concentrated to give the title compound (2.6g) as an oil. T.l.c. (System E 80:20:1) Rf 0.31

Intermediate 39

3-[2-[(6-Bromohexyl)oxy]ethoxy]pyridine

A mixture of 2-[(3-pyridinyl)oxy]ethanol (1.9g), 1,6-dibromohexane (6mℓ), tetra-n-butylammonium bisulphate (0.5g) and 50%w/v sodium hydroxide (20mℓ) was stirred vigorously for 5h, diluted with water (30mℓ) and extracted with ethyl acetate (3 x 50mℓ). The combined organic extracts were dried and evaporated in vacuo to give an oil which was purified by FCC eluting with hexane→ethylacetate to give the title compound (2.3g) as an oil. T.l.c. (System E 80:20:1) Rf 0.63

Intermediate 40

N-[6-[2-[(3-Pyridinyl)oxy]ethoxy]hexyl]benzenemethanamine

A solution of 3-[[2-[(6-bromohexyl)oxy]ethyl]oxy]pyridine (2g) and benzylamine (10mℓ) was stirred at 140° under nitrogen for 3h. The solution was partitioned between 8% sodium bicarbonate (100mℓ) and ethylacetate (100mℓ). The organic extract was dried and distilled to give the title compound (1.8g) as an oil. T.l.c. (System B 80:20:1) Rf 0.54

Intermediate 41

[4-Amino-3,5-dichloro-α-[[[3-[2-(3-phenoxypropoxy)ethoxy]propyl]-(phenylmethyl)amino]methyl]-benzenemethanol

1-[4-Amino-3,5-dichlorophenyl]-2-bromoethanone (0.95g), N-[3-[2-(3-phenoxypropoxy)ethoxy]propyl]-benzenemethanamine (1.15g) and DEA (0.48g) were stirred together in THF (35mℓ) at room temperature under nitrogen for 7h. The mixture was filtered and the filtrate evaporated in vacuo. The residue was dissolved in methanol (35mℓ) and treated portionwise with sodium borohydride (0.34g,) at 0°C under

nitrogen, stirred at room temperature for 18h, diluted with water (150m t) and the solvent evaporated in vacuo. The residue was extracted with ethyl acetate (2x150m t), dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System H (95:5:1) gave the title compound (1.30g) as an oil. T.l.c. (System H 90:10:1) Rf 0.39

Intermediate 42

4-Amino-3,5-dichloro-α-[[(phenylmethyl)[3-[2-(3-phenylpropoxy)ethoxy]propyl]amino]methyl]-benzenemethanol

1-[4-Amino-3,5-dichlorophenyl]-2-bromoethanone (0.88g), N-[3-[2-(3-phenylpropoxy)ethoxy]propyl]-benzenemethanamine (1g) and DEA (0.43g) were stirred together in THF (30m t) at room temperature under nitrogen for 22h. The mixture was filtered and the filtrate evaporated in vacuo. The residue was dissolved in methanol (40m t), treated portionwise with sodium borohydride (0.31g) at 0°C under nitrogen, stirred at room temperature under nitrogen for 2h, diluted with water (150m t) and extracted with ethyl acetate (2x150m t). The dried extract was evaporated in vacuo to give an oil. Purification by FCC eluting with System F (1:1) gave the title compound (1.22g) as an oil. T.l.c. (System F 1:1) Rf 0.19

Intermediate 43

4-Amino-3,5-dichloro-α-[[phenylmethyl[6-[2-[(3-pyridinyl)oxy]-ethoxy]hexyl]amino]methyl]benzenemethane

A solution of N-[6-[2-[(3-pyridinyl)oxy]hexyl]benzenemethanamine (18g), 1-(4-amino-3,5-dichlorophenyl)-2-bromoethanone (1.7g) and DEA (0.8g) in THF (20m t) was stirred under nitrogen overnight. The resulting precipitate was removed by filtration, the solvent evaporated and the residue dissolved in methanol (50m t), and the solution cooled in an ice bath and treated portionwise with sodium borohydride (1.2g). After 3h, the solution was concentrated in vacuo to give an oil. The oil was partitioned between water (70m t) and ethyl acetate (70m t), the organic layer was washed with brine (70m t), dried and concentrated to give an oil. Purification by FCC eluting with System G (95:5:1) gave the title compound (1.7g) as an oil. T.l.c. (System E 90:20:1) Rf 0.61

Intermediate 44

2-[(2-Phenylethyl)thio]ethanol

Phenethylmercaptan (2.0g) and potassium hydroxide (0.81g) in methanol (15m t) were stirred together under nitrogen for 15min. 2-Chloroethanol (2.33g) was added and the solution stirred under nitrogen for 6h. 2N hydrochloric acid was added to acidify the mixture of pH5, and the methanol evaporated in vacuo. The residue was partitioned between water (100m t) and diethyl ether (100m t) and separated. The aqueous phase was re-extracted with diethyl ether (100m t) and the combined ethereal layers dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System F (3:1) gave the title compound (1.80g) as a colourless oil. T.l.c. (diethyl ether) Rf 0.70

Intermediate 45

[2-[[2-[(4-Bromobutyl)oxy]ethyl]thio]ethyl]benzene

A mixture of 2-[(2-phenylethyl)thio]ethanol (1.0g), 1,4-dibromobutane (3.79g), TAB (0.6g) and 50% aqueous sodium hydroxide (12m t) was stirred at room temperature under nitrogen for 20h. The mixture was diluted with water (100m t), extracted with diethyl ether (2x100m t), dried and evaporated in vacuo to give an oil. Purification by FCC eluting with cyclohexane followed by System B (5:95) gave the title compound (1.34g) as a colourless oil. T.l.c. (System F 3:1) Rf 0.62.

Intermediate 46

2-[2-[2-(Phenylmethoxy)ethoxy]ethyl]pyridine

Sodium hydride (80% dispersion in oil, 1.68g) was added portionwise to a solution of 2-pyridineethanol (6.88g) in 1,2-dimethoxyethane (50m t) and stirred under nitrogen for 18h at room temperature. A solution of 2-(phenylmethoxy)ethanol methanesulphonate (8.25g) in 1,2-dimethoxyethane (100m t) was added and the mixture stirred at room temperature for 7h, then poured into water (400m t) and extracted with diethyl ether (3x200m t). The ethereal extracts were washed with 2N hydrochloric acid (250m t). The aqueous phase was re-extracted with diethyl ether (100m t) and the aqueous phase carefully basified with 8% sodium bicarbonate to pH8. Extraction with diethyl ether (2x200m t) and drying and evaporation in vacuo of the organic extracts gave an oil. Purification by FCC eluting with System F (4.1→1.1) gave the title compound (2.71g) as an oil. T.l.c. (diethyl ether Rf 0.54

Intermediate 47

2-[2-(2-Pyridinyl)ethoxy]ethanol hydrochloride

A solution of 2-[2-[2-(phenylmethoxy)ethoxy]pyridine (2.0g) in absolute ethanol (60m t) and ethanolic hydrochloric acid (1:9 HCl:EtOH 7.07m t) was hydrogenated over pre-reduced 10% palladium oxide on charcoal catalyst (50% aqueous, 600mg) until the uptake of hydrogen ceased (16h). The mixture was filtered and evaporated in vacuo to give the title compound (1.66g) as an oil which solidified on standing. T.l.c. (System G 95:5:1) Rf 0.08

Intermediate 48

2-[2-[2-[(6-Bromohexyl)oxy]ethoxy]ethyl]pyridine

A mixture of 2-[2-(2-pyridinyl)ethoxy]ethanol hydrochloride (1.55g), 1,6-dibromohexane (5.94g), TAB (0.5g) and 50% sodium hydroxide (15m t) was stirred at room temperature under nitrogen for 5h. The mixture was diluted with water (100m t), extracted with diethyl ether (2x150m t) and evaporated in vacuo to give an oil. The residual oil was partitioned between 2N hydrochloric acid (100m t) and hexane (2x100m t). The aqueous phase was basified to pH12 with 50% sodium hydroxide, extracted with diethyl ether (2x150m t), dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System F (2:1→1:1) gave the title compound (1.62g) as a colourless oil. T.l.c. (diethyl ether) Rf 0.40

Intermediate 49

N-[8-[2-[2-(2-Pyridinyl)ethoxy]ethoxy]hexyl]benzenemethanamine

A solution of 2-[2-[2-[(6-bromohexyl)oxy]ethoxy]ethyl]pyridine (1.55g) in benzylamine (3.1g) was heated at 125° under nitrogen for 3h. The solution was allowed to cool and then partitioned between 8% sodium bicarbonate (100m*t*) and diethyl ether (2x100m*t*). The solvent was evaporated in vacuo and the residual oil distilled (Kugelrohr) to remove excess benzylamine. Purificiation by FCC eluting with System G 92:8:1) gave the title compound (1.38g) as a colourless oil. T.l.c. (System G 95:5:1) Rf 0.14

Intermediate 50

4-Amino-3,5-dichloro-α-[[[6-[2-[2-(2-pyridinyl)ethoxy]ethoxy]hexyl](phenylmethyl)amino]methyl]-benzenemethanol

1-[4-Amino-3,5-dichloro]-2-bromoethanone (0.99g), N-[6-[2-[2-(2-pyridinyl)ethoxy)ethoxy]hexyl]-benzenemethanamine (1.25g) and DEA (0.50g) were stirred together in THF (35m*t*) at room temperature under nitrogen for 20h. The mixture was filtered and the filtrate evaporated in vacuo. The residue was dissolved in methanol (20m*t*) and sodium borohydride (0.36g) was added portionwise to the solution at 0°C under nitrogen. The mixture was stirred at room temperature for 1h and then water (10m*t*) was carefully added and the solvent evaporated in vacuo. The residue was partitioned between water (100m*t*) and ethyl acetate (100m*t*). The aqueous phase was re-extracted with ethyl acetate (100m*t*) and the combined organic phases dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System G (98:2:1) gave the title compound (1.19g) as a colourless oil. T.l.c. (System G 95:5:1) Rf 0.24

Intermediate 51

2-[[2-(2-Pyridinyl)ethyl]thio]ethanol

2-Pyridineethanethiol (1.9g) and potassium hydroxide (0.77g) in methanol (15m*t*) were stirred under nitrogen for 15min. 2-Chloroethanol (1.10g) was added and the solution stirred under nitrogen for 6h. The mixture was acidified to pH5 with 2N hydrochloric acid and then left overnight. The methanol was evaporated in vacuo and the residue partitioned between water (150m*t*) and diethyl ether (150m*t*), separated and the aqueous phase re-extracted with diethyl ether (100m*t*). The combined ethereal layers were dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System G (98:2:1) gave the title compound (0.56g) as a colourless oil. T.l.c. (diethyl ether) Rf 0.21

Intermediate 52

2-[2-[[2-[(6-Bromohexyl)oxy]ethyl]thio]ethyl]pyridine

A mixture of 2-[[2-(2-pyridinyl)ethyl]thio]ethanol (0.50g), 1,6-dibromohexane (2.13g), TAB (0.4g) and 50% aqueous sodium hydroxide (6m*t*) was stirred under nitrogen for 6h, then diluted with water (75m*t*) and extracted with diethyl ether (2x150m*t*). The organic extracts were evaporated in vacuo to give an oil, which was partitioned between 2N hydrochloric acid (100m*t*) and hexane (2x100m*t*). The aqueous phase was basified to pH 12 with 50% aqueous sodium hydroxide and extracted with diethyl ether (2x150m*t*), the dried organic extracts were evaporated in vacuo to give an oil. Purification by FCC eluting with System F (1:1) gave the title compound (0.60g) as a colourless oil. T.l.c. (diethyl ether) Rf 0.64

Example 1

4-Hydroxy-α'-[[[6-(4-phenoxy)butoxy)hexyl]amino]methyl] -1,3-benzenedimethanol

Intermediate 1 (2g), [4-[(6-bromohexyl)oxy]butoxy]benzene (3g) and DEA (2.3ml) in DMF (30ml) were stirred at 100° for 2h. Saturated aqueous sodium bicarbonate (80ml) was added and the mixture extracted with ethyl acetate (3x100ml). The combined organic extracts were washed with water (50ml), dried and evaporated. The resulting orange oil was applied to an FCC column and eluted with System D (89:10:1) to give an orange paste. Trituration with cyclohexane gave the title compound (1.7g) as a brown solid m.p. 60-68°. T.l.c. (System D 60:10:1) Rf 0.35.

Example 2

4-Hydroxy-α'-[[[6-[3-(phenylthio)propoxy]hexyl]amino] methyl]-1,3-benzenedimethanol

[[3-[(6-Bromohexyl)oxy]propyl]thiobenzene (2.0g), Intermediate 1 (1.51g), DEA (1.71ml) and DMF (22ml) were stirred at 100° under nitrogen for 1h. The cooled mixture was evaporated under reduced pressure and treated with aqueous saturated sodium bicarbonate (80ml). The mixture was extracted with ethyl acetate (2x100ml), and the combined extracts were washed with water (100ml). The dried organic layer was evaporated and the residue in methanol (20ml) was evaporated onto silica gel (Merck, 7734 10g). The resultant silica gel plug was applied to an FCC column and elution with System D (89:10:1) afforded, after trituration with ethyl acetate, the title compound (617mg) as a cream solid m.p. 89-92°. T.l.c. (System D 90:10:1) Rf 0.14.

Example 3

4-Hydroxy-α'-[[[6-[2-phenoxyethoxy)hexyl]amino]methyl]-1,3-benzenedimethanol

Intermediate 1 (0.9g), [2-[(6-bromohexyl)oxy]ethoxy]benzene (1.65g) and DEA (1.2mℓ) in DMF (20mℓ) were stirred at 75° for 3h. The solution was evaporated under reduced pressure and the resulting amber syrup (3.6g) was partitioned between ethyl acetate and 8% sodium bicarbonate solution (100mℓ). The organic extract was washed with water, the aqueous solutions were re-extracted with ethyl acetate (2x50mℓ) and the combined organic extracts dried and evaporated. The residual yellow oil (2.04g) was purified by FCC eluting with ethyl acetate and System D (85:15:1) to give a colourless oil (0.9g). Further elution with the latter solvent mixture afforded the title compound (0.75g) as a colourless oil, which when triturated with diethyl ether gave a white solid (0.45g) m.p. 67-68°.
Found: C,68.27;H,8.39;N,3.37.
$C_{23}H_{33}NO_5$ requires C,68.46;H,8.24;N,3.47%.

Example 4

4-Hydroxy-α'-[[[6-[(4-phenylthio)butoxy]hexyl]amino] methyl[-1,3-benzenedimethanol benzoate

A solution of [[4-[(6-bromohexyl)oxy]butyl]thio]benzene (1g) in DMF (5mℓ) was added dropwise to a stirred solution of Intermediate 1 (0.64g) and DEA (1.24g) in DMF (25mℓ) at 70° under nitrogen. The solution was stirred at 70° under nitrogen for 2.5h and evaporated in vacuo onto FCC silica. Purification by FCC eluting with System E (39:10:1) gave a colourless oil, which was dissolved in methanol (10mℓ) and

treated with benzoic acid (0.2g). The solvent was evaporated and the residual oil triturated with diethyl ether to give the title compound (0.57g) as a cream solid m.p. 108-110°.
Found: C,67.4; H,7.7; N,2.5.
$C_{25}H_{37}NO_4S.C_7H_6O_2$ requires C,67.5; H,7.6; N,2.5%.

Example 5

4-Hydroxy-α'-[[[5-[3-[(4-methoxy)phenoxy]propoxy]-1-methylpentyl]amino]methyl]-1,3-benzenedimethanol benzoate

A solution of intermediate 1 (0.33g) and 6-[3-[4-(methoxy)phenoxy]propoxy]-2-hexanone (0.5g) in absolute ethanol (25mℓ) was hydrogenated over a mixture of pre-reduced 5% platinum oxide on charcoal (250mg) and 10% palladium oxide on charcoal (250mg) catalysts in absolute ethanol (10mℓ). The mixture was filtered and evaporated in vacuo to give a product which was purified by FCC, elution with System E (3g:10:1) affording an oil. This was dissolved in methanol (5mℓ) and treated with benzoic acid (0.03g), evaporated and triturated with diethyl ether to give the title compound (0.11g) as a pale brown foam.
Found: C,65.05; H,7.63; N,2.37.
$C_{25}H_{37}NO_6.C_7H_6O_2.H_2O$ requires C,65.39; H,7.55; N,2.38%.
T.l.c. (System E 39:10:1) Rf 0.23.

Example 6

Propyl 4-[3-[[6-[[2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino]hexyl]oxy]propoxy] benzoate

Propyl 4-[3-[(6-bromohexyl)oxy]propoxy]benzoate (0.80g) was added dropwise over 10 mins to a solution of intermediate 1 (0.55g) and DEA (0.56g) in DMF (10mℓ) stirred at 80° under nitrogen. The solution was stirred at 80° for a further 2h, the solvent removed in vacuo at 80° and the residual oil partitioned between water (50mℓ) and ethyl acetate (50mℓ). The aqueous phase was extracted with further ethyl acetate (50mℓ), the combined organic layers were dried and concentrated to yield a product which was purified by FCC, elution with System E (39:10:1) yielding the title compound (0.33g) as a viscous colourless oil which solidified to a white powder on trituration with diethyl ether m.p. 75-78°.
Found: C,66.74; H,8.30; N,2.86.
$C_{28}H_{41}NO_7$ requires C,66.78; H,8.21; N,2.78%.

Example 7

4-Hydroxy-α'-[[[6-[3-[(4-methylphenyl)thio]propoxy]hexyl] amino]methyl]-1,3-benzenedimethanol hydrobromide

A solution of 1-[[[3-[(6-bromohexyl)oxy]propyl]thio]-4-methylbenzene (1g) in DMF (5mℓ) was added dropwise to a stirred solution of intermediate 1 (0.64g) and DEA (1.24g) in DMF (25mℓ) at 70° under nitrogen. The solution was stirred at 70° under nitrogen for 2h and evaporated in vacuo onto FCC silica. Purification by FCC on triethylamine deactivated silica (Merck 9385) eluting with toluene-ethanol (8:1) gave a colourless oil, which on trituration with diethyl ether gave the title compound (0.3g) as a white solid m.p. 74-76°.
Found: C,57.3; H,7.4; N,2.7.
$C_{25}H_{37}NO_4S.HBr$ required C,56.8; H,7.25; N,2.65%.

Example 8

α'-[[[6-[2-(3,4-Dimethylphenoxy)ethoxy]hexyl]amino]methyl] -4-hydroxy-1,3-benzenedimethanol

A solution of [2-[(6-bromohexyl)oxy]ethoxy]-3,4-dimethylbenzene (1.82g), Intermediate 1 (0.9g) and DEA (1.2mℓ) in DMF (20mℓ) was stirred at 70° for 3h, evaporated under reduced pressure and the residual brown gum was extracted into 8% sodium bicarbonate solution (50mℓ) and ethyl acetate (3x50mℓ). The dried ethyl acetate solution was evaporated under reduced pressure and the residual oil (1.9g) was purified by FCC. Elution with ethyl acetate followed by System D (85:15:1) gave an amber oil (0.55g) which was triturated with diethyl ether (2x30mℓ). Evaporation of the ethereal solution gave the title compound (0.14g) as a white solid m.p. 65-68°.
Assay Found: C,69.39; H,8.79; N,3.12.
$C_{25}H_{37}NO_5$ requires C,69.58; H,8.64; N,3.25%.

Example 9

α'-[[[5-[2-(4-Chlorophenylthio)ethoxy]pentyl]amino]methyl] -4-hydroxy-1,3-benzenedimethanol

A solution of [[2-[(5-bromopentyl)oxy]ethyl]thio]-4-Chlorobenzene (1.85g), Intermediate 1 and DEA (1.2mℓ) in DMF (20mℓ) was stirred for 70° for 3h, evaporated under reduced pressure and the residual amber oil treated with 8% sodium bicarbonate solution (50mℓ) and water (50mℓ). The mixture was extracted with ethyl acetate (3x100mℓ) which was dried and evaporated. The resulting liquid (2.25g) was purified by FCC eluting with ethyl acetate followed by System D (85:15:1) to give an oil (0.6g) which then treated with diethyl ether gave the title compound (0.5g) as a white solid m.p. 69-73°
Assay Found : C,60.06; H,6.93; N,3.05.
$C_{22}H_{30}ClNO_4S$ requires C,60.05; H,6.87; N,3.18%.

Example 10

4-[3-[[6-[[2-(4-Amino-3,5-dichlorophenyl)-2-hydroxyethyl] amino]hexyl]oxy]propoxy]-N,N-diethylbenzamide (E)-butenedioate

4-[3-[[6-[[2-(4-Amino-3,5-dichlorophenyl)-2-hydroxyethyl](phenylmethyl)amino]hexyl]oxy]propoxy]-N,N-diethylbenzamide (1.45g) was hydrogenated over pre-reduced 10% palladium on carbon (50% aqueous paste, 310mg) in ethanol-(15mℓ) containing hydrochloric acid (conc. HCl/EtOH, 1:9v/v, 2.1mℓ). The catalyst was removed by filtration the solvent was evaporated and the residue was partitioned between 8% sodium bicarbonate (20mℓ) and ethyl acetate (20mℓ). The aqueous layer was re-extracted with ethyl acetate (20mℓ) and the combined organic extracts were washed with 8% sodium bicarbonate and brine, dried and concentrated to a slightly coloured oil which was purified by FCC eluting with System G (90:10:1) to give a colourless oil (840mg). A solution of the oil (810mg) and fumaric acid (180mg) in methanol (10mℓ) was concentrated to an oil which was triturated several times with diethyl ether to give the title compound - (670mg) as an off white powder. T.l.c. (System E 80:20:2) Rf 0.56.
Analysis Found : C,58.66; H,6.99; N,6.60; C1,11.96.
$C_{28}H_{41}Cl_2N_3O_4.0.5C_4H_4O_4$ requires C,58.82; H,7.08; H,7.08; N,6.86; Cl,11.57%.

Example 11

N,N-Diethyl-4-[3-[[6-[[2-[4-hydroxy-3-[(methylsulphonyl)amino]phenyl]-ethyl]amino]hexyl]oxy]-propoxy]-benzamide benzoate

A solution of N-[5-(bromoacetyl)-2-(phenylmethoxy)phenyl]-methanesulphonamide (1.5g), N, N-diethyl-4-[3-[[6-[(phenylmethyl)-amino]hexyl]oxy]propoxy]benzamide (1.56g) and DEA (0.54g) in dichloromethane (35m ℓ) was stirred at room temperature under nitrogen for 4h. The solvent was evaporated and the residual oil in ethanol (130m ℓ) was hydrogenated over pre-reduced 10% palladium on charcoal (50% paste in water, 0.7g) and 5% platinum on charcoal (0.8g). The reaction mixture was filtered and the solvent was evaporated. The residual oil was purified by FCC eluting with System E (80:20:2) to give a foam (544mg) which was dissolved in methanol (5m ℓ) and treated with benzoic acid (124mg) in methanol (5m ℓ). The solution was concentrated and the residue was triturated with diethyl ether for five days to give the title compound (510mg) as a white solid, m.p. 75-77°.
Analysis Found : C,60.8; H,7.5; N,5.9;S,4.6.
$C_{29}H_{45}N_3O_7S.C_7H_8O_2.0.5H_2$) requires C,60.8; H,7.4; N,5.9;

Example 12

4-Hydroxy-α¹-[[[3-[2-(4-phenylbutoxy)ethoxy]propyl]amino]methyl]-1,3-benzenedimethanol benzoate

[4-[2-(3-Bromopropoxy)ethoxy]butyl]benzene (2.0g) was added dropwise to Intermediate 1 (1.3g) and DEA (1.7g) in DMF (20m ℓ) at 70°. The solution was heated at 70-75° for 2h and evaporated, and the residue was purified by FCC eluting with System E (80:20:1) to give a yellow gum. The gum (0.8g) in chloroform was treated with benzoic acid (0.6g) and evaporated. The residue was triturated with diethyl ether (2x50m ℓ) to give the title compound (0.9g) as a yellow gum. T.l.c. (System E 80:20:1) Rf 0.5
Analysis Found: C,68.7; H,7.8; N,2.4.
$C_{24}H_{35}NO_5.C_7H_8O_2$ requires C,69.0; H,7.7; N,2.6%.

Example 13

4-Amino-3,5-dichloro-α-[[[3-[2-(3-phenoxypropoxy)ethoxy]propyl]amino] methyl]benzenemethanol (E)-2-butenedioate

[4-Amino-3,5-dichloro-α-[[[3-[2-(3-phenoxypropoxy)ethoxy]propyl](phenylmethyl)amino]methyl]-benzenemethanol (1.2g) was hydrogenated over pre-reduced 10% palladium oxide on charcoal catalyst (50% aqueous, 220mg) in ethanol (15m ℓ) containing hydrochloric acid (1:9 conc. hydrochloric acid/ethanol, 1.99m ℓ) until the uptake of hydrogen (54m ℓ) ceased. The mixture was filtered and evaporated in vacuo. The resulting brown oil was dissolved in ethyl acetate (100m ℓ) and basified with 8% sodium bicarbonate solution (150m ℓ). The aqueous phase was re-extracted with ethyl acetate (50m ℓ) and the combined organic phases were dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System H (90:10:1 → 90:20:1) gave a colourless oil (0.55g). This was dissolved in methanol (15m ℓ), treated with fumaric acid (0.07g), evaporated in vacuo and triturated with diethyl ether to give the title compound (0.52g) as a white solid; m.p. 97-98.5°. T.l.c. (System E 40:10:1) Rf 0.21

Example 14

4-Amino-3,5-dichloro-α-[[[3-[2-(3-phenylpropoxy)ethoxy]propyl]amino] methyl]benzenemethanol (E)-butenedioate

A solution of [4-amino-3,5-dichloro-α-[[(phenylmethyl)[3-[2-(3-phenylpropoxy)ethoxy]propyl]amino]-methyl]benzenemethanol (1.10g) and 1:9 conc. hydrochloric acid in ethanol (1.88mℓ) in absolute ethanol (16mℓ) was hydrogenated over pre-reduced 10% palladium oxide on charcoal (50% aqueous paste 210mg) in absolute ethanol (5mℓ) until the uptake of hydrogen (56.9mℓ) ceased. The mixture was filtered and evaporated in vacuo to give a brown oil (1.09g). Trituration with diethyl ether gave a solid, which was dissolved in ethyl acetate (150mℓ) and basified with 8% sodium bicarbonate solution (100mℓ). The aqueous phase was re-extracted with ethyl acetate (50mℓ) and the combined organic phases dried and evaporated in vacuo. The resulting brown oil, (0.27g) was dissolved in methanol (10mℓ) and treated with fumaric acid (0.04g). The solution was evaporated in vacuo and the residue triturated with diethyl ether to give the title compound (0.32g) as a white solid m.p. 89.5-91° T.l.c. (System E 40:10:1) Rf 0.42

Example 15

4-Amino-3,5-dichloro-α-[[[6-[2-[(3-pyridinyl)oxy]ethoxy]hexyl]amino]methyl]benzenemethanol (E)-butenedioate

4-Amino-3,5-dichloro-α-[[(phenylmethyl)[6-[2-[(3-pyridinyl)oxy]ethoxy]hexyl]amino]methyl]-benzenemethanol (1g;) was hydrogenated over pre-reduced palladium oxide on carbon (50% aqueous paste, 200mg) in ethanol (30mℓ) containing conc. hydrochloric acid for 6h (uptake of hydrogen, 45mℓ). The catalyst was removed by filtration the solvent was evaporated and the residual oil was partitioned between 8% sodium bicarbonate (50mℓ) and ethyl acetate (50mℓ). The organic layer was dried and concentrated to give a yellow oil which was purified by FCC eluting with System G (95:5:1) to give an oil (590mg). The oil was dissolved in methanol (20mℓ) and treated with fumaric acid (77mg) and concentrated to give a foam which was triturated in ethyl acetate to give the title compound (650mg) as a white solid - m.p. 105-106° T.l.c. (System E 90:20:1) Rf 0.34

Example 16

[4-Amino-3,5-dichloro-α-[[[4-[2-[(2-phenylethyl)thio]ethoxy]butyl] amino]methyl]benzenemethanol

A solution of 4-amino-α-(aminomethyl)-3,5-dichlorobenzenemethanol (1.53g), [2-[[2-(4-bromobutoxy)-ethyl]thio]ethyl]benzene (1.0g) and DEA (0.71g in DMF (20mℓ) was stirred under nitrogen at 100° for 2h. The solvent was evaporated in vacuo and the residue purified by FCC eluting with System G (95:5:1) to give an oil. The oil was partitioned between dichloromethane (50mℓ) and 8% sodium bicarbonate (75mℓ) and the aqueous solution re-extracted with dichloromethane (50mℓ). The organic extracts were dried and evaporated in vacuo to give the title compound (924mg,) as a white solid m.p. 74-77°. T.l.c. (System E 40:10:1) Rf 0.57

Example 17

4-Amino-3,5-dichloro-α-[[[6-[2-[2-(2-pyridinyl)ethoxy]ethoxy]hexyl]-amino]methyl]benzenemethanol

A solution of 4-amino-3,5-dichloro-α-[[(phenylmethyl)[6-[2-[2-(2-pyridinyl)ethoxy]ethoxy]hexyl]amino]-methyl]benzenemethanol (1.1g,) in ethanol (25mℓ) was hydrogenated over pre-reduced 10% palladium oxide on charcoal catalyst (50% aqueous paste, 800mg) in ethanol (10mℓ) containing 1:9 conc. hydrochloric

acid/ethanol, (1.78m.t.,) until the uptake of hydrogen ceased (1h). The mixture was filtered and evaporated in vacuo to give an oil which was dissolved in dichloromethane (100m.t) and washed with 8% sodium bicarbonate (50m.t). The aqueous phase was re-extracted with dichloromethane (50m.t) and the combined organic phases dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System G (95:5:1) gave a colourless oil, which was dissolved in methanol (10m.t) and treated with fumaric acid (0.09g), evaporated in vacuo and triturated with diethyl ether to give a white solid (0.75g,). The solid was dissolved in dichloromethane (150m.t) and washed with 8% sodium bicarbonate (100m.t). The aqueous layer was re-extracted with dichloromethane (100m.t) and the combined organic fractions dried and evaporated in vacuo to give an oil. Trituration with System F (ca. 10:1) gave the title compound (0.60g.) as a white solid m.p. 45.5-46.5° T.l.c. (System E 40:10:1) Rf 0.49

Example 18

[4-Amino-3,5-dichloro-α-[[[6-[2-[[2-(2-pyridinyl)ethyl]thio]ethoxy]hexyl]amino]methyl]benzenemethanol

A solution of 4-amino-α-(aminomethyl)-3,5-dichlorobenzenemethanol (0.58g,), 2-[2-[[2-[(6-bromohexyl)-oxy]ethyl]thio]ethyl]pyridine (0.58g,) and DEA (0.26g,) in DMF (10m.t) was stirred under nitrogen for 2h. The solvent was evaporated in vacuo and the residual oil partitioned between 8% sodium bicarbonate solution (100m.t) and dichloromethane (100m.t). The aqueous phase was re-extracted with dichloromethane (100m.t) and the combined organic phases dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System G (98:2:1) gave an oil. Trituration with hexane afforded the title compound - (451mg,) as a solid m.p. 59.5-62° T.l.c. (System E 40:10:1) Rf 0.32

The following are examples of suitable formulations of compounds of the invention. The term 'active ingredient' is used herein to represent a compound of the invention.

Tablets (Direct Compression)

	mg/tablet
Active ingredient	2.0
Microcrystalline cellulose USP	196.5
Magnesium Stearate BP	1.5
Compression weight	200.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using 7mm diameter punches.

Table of other strengths may be prepared by altering the ratio of active ingredient to microcrystalline cellulose or the compression weight and using punches to suit.

The tablets may be film coated with suitable film forming materials, such as hydroxypropylmethylcellulose, using standard techniques. Alternatively, the tablets may be sugar coated.

Metered Dose Pressurised Aerosol (Suspension Aerosol)

	mg/metered dose	Per can
Active ingredient micronised	0.100	26.40mg
Oleic Acid BP	0.010	2.64mg
Trichlorofluoromethane BP	23.64	5.67g
Dichlorodifluoromethane BP	61.25	14.70g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The oleic acid is mixed with the trichlorofluoromethane at a temperature of 10-15°C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves delivering 85mg of suspension are crimped onto the cans and the dichlorodifluoromethane is pressure filled into the cans through the valves.

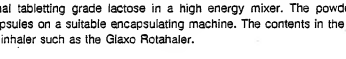
Inhalation Cartridges

	mg/cartridge
Active ingredient micronised	0.200
Lactose BP to	25.0

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents in the cartridges are administered using a powder inhaler such as the Glaxo Rotahaler.

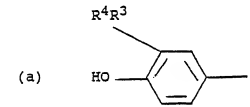
Claims

1. Compounds of the general formula (I)



(I)

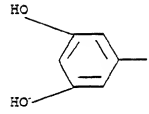
and physiologically acceptable salts and solvates thereof wherein
Ar represents



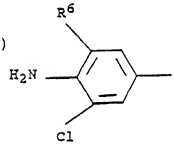
(a)

where
R^3 is a bond or a straight or branched C_{1-2}alkylene group,
R^4 is a hydroxy group or a group R^5NH-where
R^5 represents a group CH_3SO_2-, HCO-or NH_2CO-,

(b)

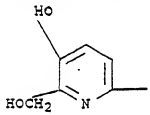


(c)

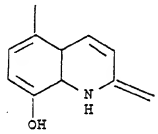


where R^6 is a chlorine atom or the group F_3C-,

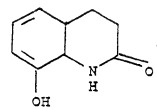
(d)



(e)



or



k represents an integer from 1 to 8,

m represents zero or an integer from 2 to 7 and

n represents an integer from 2 to 7 with the proviso that the sum total of k, m and n is 4 to 12;

R^1 and R^2 each represents a hydrogen atom or a methyl or ethyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 2;

R^{30} represents hydrogen or C_{1-2}alkyl;

X represents an oxygen or sulphur atom; and

Y and Q may each represent a bond or an oxygen or sulphur atom with the provisos that at least one of Y and Q represents an oxygen or sulphur atom and when Y is a bond m is zero, or when Y represents an oxygen or sulphur atom m is an integer from 2 to 7;

P represents a phenyl group optionally substituted by one or more substituents selected from halogen atoms, or the groups C_{1-3}alkyl, C_{1-3}alkoxy, hydroxy, $-CH_2OH$-, $-(CH_2)_2OH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2(CH_2)_2CH_3$, $-R^7$, COR^7, $-NHCOR^8$ and $NR^9SO_2R^{10}$;

where

R^7 represents an amino, aminoC_{1-3}alkyl, aminoC_{1-3}dialkyl, pyrrolidino, piperidino, hexamethyleneimino,

piperazino, N-methylpiperazino or morpholino group;
R^8 represents a hydrogen atom or a C_{1-4}alkyl, C_{1-4}alkoxy, phenyl or amino group;
R^9 represents a hydrogen atom or a methyl group;
R^{10} represents a methyl, phenyl, amino or dimethylamino group:
or P represents a pyridyl group optionally substituted by one or two substitutents selected from halogen atoms or hydroxy, C_{1-3}alkyl and C_{1-3}alkoxy groups.

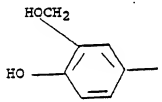
2. Compounds as claimed in claim 1 wherein the chain $-(CH_2)_k-$is a group selected from $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$and $-(CH_2)_7-$and the chains $-(CH_2)_m-$and $-(CH_2)_n-$are each groups selected from $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$and $-(CH_2)_6-$, or the chain $-(CH_2)_m$ is a bond, subject to the proviso that the sum total of k, n and m is 4 to 12.

3. Compounds as claimed in claim 1 or 2 wherein the sum total of carbon atoms in the chains $-(CH_2)_k-$, $-(CH_2)_m-$and $-(CH_2)_n-$is 7, 8 or 9.

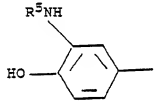
4. Compounds as claimed in any of claims 1 to 3 wherein R^1 and R^2 are each a hydrogen atom or a methyl group.

5. Compounds as claimed in any of claims 1 to 4 wherein R^{30} is a hydrogen atom.

6. Compounds as claimed in any of claims 1 to 5 wherein Ar is a group of type b), c) or d) as defined in claim 1 or a group of formula

f) 

or

i) 

where R^5 is HCO-, NH_2CO-or CH_3SO_2-.

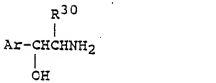
7. Compounds as claimed in any of claims 1 to 6 wherein P is an optionally substituted phenyl group containing one or two substituents selected from halogen atom(s), C_{1-5}alkyl and C_{1-5}alkoxy groups and the groups $-CO_2(CH_2)_2CH_3$, $-CON(CH_2CH_3)_2$ and $NHCOCH_3$ or a pyridyl group attached to the rest of the molecule at the 2-, 3-or 4-position, and optionally containing a single substituent selected from hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy or halogen.

8. Compounds as claimed in any of claims 1 to 7 in which X represents an oxygen atom and one of Y and Q represents an oxygen or sulphur atom and the other represents a bond or X, Y and Q all represent oxygen atoms.

9. 4-Hydroxy-α^1-[[[6-[(4-phenylthio)butoxy]hexyl]amino]methyl]-1,3-benzenedimethanol,
4-[3-[[6-[[2-(4-amino-3,5-dichlorophenyl)-2-hydroxyethyl]amino]hexyl]oxy]propyl]-N,N-diethylbenzamide,
4-hydroxy-α^1-[[[3-[2-(4-phenylbutoxy)ethoxy]propyl]amino]methyl]-1,3-benzenedimethanol,
4-amino-3,5-dichloro-α-[[[3-[2-(3-phenoxypropoxy)ethoxy]propyl]amino]methyl]benzenemethanol,
4-amino-3,5-dichloro-α-[[[3-[2-(3-phenylpropoxy)ethoxy]propyl]amino]methyl]benzenemethanol,
[4-amino-3,5-dichloro-α-[[[6-[2-[[2-(2-pyridinyl)ethyl]thio]ethoxy]hexyl]amino]methyl]benzenemethanol
4-hydroxy-α^1-[[[3-[2-[3-(4-acetamido)phenylpropoxy]ethoxy]propyl]amino]methyl]-1,3-benzenedimethanol
and physiologically acceptable salts and solvates thereof.

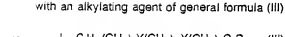
10. A process for the preparation of compounds of formula (I) as defined in any of claims 1 to 9 which comprises:

(1a) for the preparation of compounds of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (II)



(II)

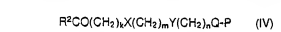
with an alkylating agent of general formula (III)



(III)

where L represents a leaving group, followed where necessary by removal of any protecting groups; or

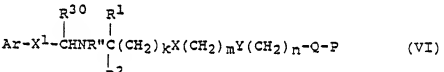
(1b) for the preparation of compounds of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (II) with a compound of general formula (IV)



(IV)

in the presence of a reducing agent, followed where necessary by removal of any protecting groups; or

(2) reducing an intermediate of general formula (VI)



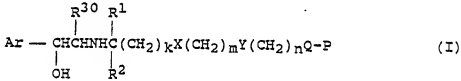
(VI)

where X^1 represents a reducible group and $R^{\prime}$ represents a hydrogen atom or a protecting group, followed where necessary by removal of any protecting groups; and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer; and/or where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

11. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof together with at least one physiologically acceptable carrier or excipient.

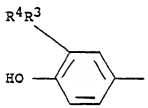
Claims for the following contracting states: GR, ES.

1. A process for the preparation of compounds of the general formula (I)



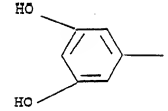
(I)

and physiologically acceptable salts and solvates thereof wherein Ar represents (a)

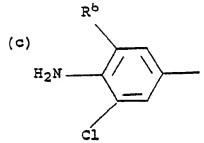


where
R^3 is a bond or a straight or branched C_{1-2}alkylene group,
R^4 is a hydroxy group or a group R^5NH-where
R^5 represents a group CH_3SO_2-, HCO-or NH_2CO-,

(b)

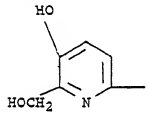


(c)

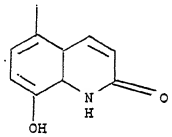


where R^6 is a chlorine atom or the group F_3C-.

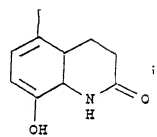
(d)



(e)



or



k represents an integer from 1 to 8,
m represents zero or an integer from 2 to 7 and
n represents an integer from 2 to 7 with the proviso that the sum total of k, m and n is 4 to 12;
R^1 and R^2 each represents a hydrogen atom or a methyl or ethyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 2;
R^{30} represents hydrogen or C_{1-2}alkyl;
X represents an oxygen or sulphur atom; and
Y and Q may each represent a bond or an oxygen or sulphur atom with the provisos that at least one of Y and Q represents an oxygen or sulphur atom and when Y is a bond m is zero, or when Y represents an oxygen or sulphur atom m is an integer from 2 to 7;
P represents a phenyl group optionally substituted by one or more substituents selected from halogen

atoms, or the groups C_{1-3}alkyl, C_{1-3}alkoxy, hydroxy, $-CH_2OH$-, $-(CH_2)_2OH$, $-CO_2H$, $-CO_2CH_3$, $-CO_2(CH_2)_2CH_3$, $-R^7$, COR^7, $-NHCOR^8$ and $-NR^9SO_2R^{10}$;

where

R^7 represents an amino, aminoC$_{1-3}$alkyl, aminoC$_{1-3}$dialkyl, pyrrolidino, piperidino, hexamethyleneimino, piperazino, N-methylpiperazino or morpholino group;

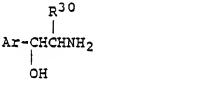
R^8 represents a hydrogen atom or a C_{1-4}alkyl, C_{1-4}alkoxy, phenyl or amino group;

R^9 represents a hydrogen atom or a methyl group;

R^{10} represents a methyl, phenyl, amino or dimethylamino group;

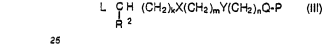
or P represents a pyridyl group optionally substituted by one or two substitutents selected from halogen atoms or hydroxy, C_{1-3}alkyl and C_{1-3}alkoxy groups, which comprises

(1a) for the preparation of compounds of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (II)



(II)

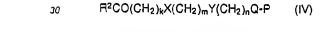
with an alkylating agent of general formula (III)



(III)

where L represents a leaving group, followed where necessary by removal of any protecting groups; or

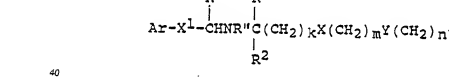
(1b) for the preparation of compounds of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (II) with a compound of general formula (IV)



(IV)

in the presence of a reducing agent, followed where necessary by removal of any protecting groups; or

(2) reducing an intermediate of general formula (VI)



(VI)

where X^1 represents a reducible group and R^a represents a hydrogen atom or a protecting group, followed where necessary by removal of any protecting groups; and when the compound of formula (I) is obtained as a mixture of enantiomers, optionally resolving the mixture to obtain the desired enantiomer; and/or where the compound of formula (I) is in the form of a free base, optionally converting the free base into a salt.

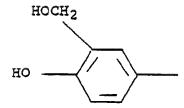
2. A process as claimed in claim 1 for the production of compounds wherein the chain $-(CH_2)_k$-is a group selected from $-CH_2$-, $-(CH_2)_2$-, $-(CH_2)_3$-, $-(CH_2)_4$-, $-(CH_2)_5$-, $-(CH_2)_6$-and $-(CH_2)_7$-and the chains $-(CH_2)_m$-and $-(CH_2)_n$-are each groups selected from $-(CH_2)_2$-, $-(CH_2)_3$-, $-(CH_2)_4$-, $-(CH_2)_5$-and $-(CH_2)_6$-, or the chain $-(CH_2)_m$ is a bond, subject to the proviso that the sum total of k, n and m is 4 to 12.

3. A process as claimed in claim 1 or 2 for the production of compounds wherein the sum total of carbon atoms in the chains $-(CH_2)_k$-, $-(CH_2)_m$-and $-(CH_2)_n$-is 7, 8 or 9.

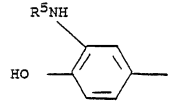
4. A process as claimed in any of claims 1 to 3 for the production of compounds wherein R^1 and R^2 are each a hydrogen atom or a methyl group.

5. A process as claimed in any of claims 1 to 4 for the production of compounds wherein R^{30} is a hydrogen atom.

6. A process as claimed in any of claims 1 to 5 for the production of compounds wherein Ar is a group of type b), c) or d) as defined in claim 1 or a group of formula

f) 

or

i) 

where R^5 is HCO-, NH_2CO-or CH_3SO_2-.

7. A process as claimed in any of claims 1 to 6 for the production of compounds wherein P is an optionally substituted phenyl group containing one or two substituents selected from halogen atom(s), C_{1-5}alkyl and C_{1-5}alkoxy groups and the groups $-CO_2(CH_2)_2CH_3$, $-CON(CH_2CH_3)_2$ and $NHCOCH_3$ or a pyridyl group attached to the rest of the molecule at the 2-, 3-or 4-position, and optionally containing a single substituent selected from hydroxy, C_{1-3}alkyl, C_{1-3}alkoxy or halogen.

8. A process as claimed in any of claims 1 to 7 for the production of compounds in which X represents an oxygen atom and one of Y and Q represents an oxygen or sulphur atom and the other represents a bond or X, Y and Q all represent oxygen atoms.

9. A process as claimed in claim 1 for the production of a compound selected from:
4-hydroxy-α'-[[[6-[(4-phenylthio)butoxy]hexyl]amino]methyl]-1,3-benzenedimethanol,
4-[3-[[6-[[2-(4-amino-3,5-dichlorophenyl)-2-hydroxyethyl]amino]hexyl]oxy]propyl]-N,N-diethylbenzamide,
4-hydroxy-α'-[[[3-[2-(4-phenylbutoxy)ethoxy]propyl]amino]methyl]-1,3-benzenedimethanol,
4-amino-3,5-dichloro-α-[[[3-[2-(3-phenoxypropoxy)ethoxy]propyl]amino]methyl]benzenemethanol,
4-amino-3,5-dichloro-α-[[[3-[2-(3-phenylpropoxy)ethoxy]propyl]amino]methyl]benzenemethanol,
[4-amino-3,5-dichloro-α-[[[6-[2-[[2-(2-pyridinyl)ethyl]thio]ethoxy]hexyl]amino]methyl]benzenemethanol
4-hydroxy-α'-[[[3-[2-[3-(4-acetamido)phenylpropoxy]ethoxy]propyl]amino]methyl]-1,3-benzenedimethanol
and physiologically acceptable salts and solvates thereof.